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ORIGINAL ARTICLE

Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement

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Abstract

Although surgical resection and liver transplantation are the only treatment modalities that enable prolonged survival in patients with hepatocellular carcinoma (HCC), the majority of HCC patients presents with advanced disease and do not undergo resective or ablative therapy. Transarterial chemoembolization (TACE) is indicated in intermediate/advanced stage unresectable HCC even in the setting of portal vein involvement (excluding main portal vein). Sorafenib has been shown to improve survival of patients with advanced HCC in two controlled randomized trials. Yttrium 90 is a safe microembolization treatment that can be used as an alternative to TACE in patients with advanced liver only disease or in case of portal vein thrombosis. External beam radiation can be helpful to provide local control in selected unresectable HCC. These different treatment modalities may be combined in the treatment strategy of HCC and also used as a bridge to resection or liver transplantation. Patients should undergo formal multidisciplinary evaluation prior to initiating any such treatment in order to individualize the best available options.

Keywords

consensus conference, hepatocellular cancer, hepatoma, surgery, chemotherapy, radiotherapy, chemoembolization, liver transplantation

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Introduction

Death rates from hepatocellular cancer (HCC) in the United States have increased by 47% in males and 27% in females since 1990.[1] These data reflect a rising incidence, and only a slight improvement of five-year overall survival of 11%.[1] The majority of HCC patients present with advanced disease that is not amenable to resection or orthotopic liver transplantation (OLT); 84% with extensive intrahepatic disease do not undergo any resective or ablative therapy.[2] However, there has been an increase in the use of noninvasive local and regional therapies in recent years.[2] Several 'noncurative' therapy forms have gained traction in the management of HCC. Among these, four of the most widely employed modalities are summarized in this Consensus Statement review: transarterial chemoembolization (TACE), systemic therapy with non-chemotherapeutic agents, ^{90}Yttrium microsphere radioembolization treatment (Y90), and photon or proton radiotherapy. It is mandatory that patients undergo a formal multidisciplinaryevaluation prior to initiating any such treatment in order to balance the available options.

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The role of TACE and emerging therapies

TACE

TACE was introduced in 1977 by Yamada *et al.*, who exploited HCC's preferential blood supply from the hepatic artery to deliver

chemotherapy without damaging the surrounding liver parenchyma.[3,4] A decade later, the observation that lipiodol, an iodinated ester derived from poppy-seed oil, can be selectively taken up and retained by primary HCC and some hepatic metastases of colonic and neuroendocrine tumors led to the popularization of this compound as a component of the injected TACE cocktail.[5–7] Moreover, lipiodol effectively increases the local concentrations of chemotherapeutic agents, leading to cancer cell death by ischemia as well as by chemotherapeutic mechanisms.

Controversy persists regarding the choice of the chemotherapeutics used for TACE. Drugs including doxorubicin, epirubicin, cisplatin, mitomicin C, and mitoxantrone have been used with TACE. Currently, there is no 'best' chemotherapeutic agent. The most common chemotherapeutic drug used as a sole agent is doxorubicin, whereas the combination of cisplatin, doxorubicin, and mitomycin C is the most common combination drug regimen for embolization treatment of HCC.[8] All of these drugs have high hepatic extraction with concurrent low systemic drug exposure. Despite the favorable pharmacokinetics, most randomized controlled trials have failed to demonstrate an advantage of one agent over another.[9] In one study, cisplatin was shown to be more effective than doxorubicin as a single agent against HCC; however, this improved effectiveness could not be correlated with improved survival.[10] Some suggest that injectable volumes of chemotherapy and long-term arterial patency were improved by embolizing the tumor-feeding vessel(s) only after the entire dose of chemotherapy had been delivered.[11]

In the United States, the most common combination is the mixture of cisplatin 100 mg (Bristol Myers Squibb, Princeton, NJ), doxorubicin 50 mg (Adriamycin; Pharmacia-Upjohn, Kalamazoo, MI) and mitomycin C 10 mg (Bedford Laboratories, Bedford, OH) diluted in 10 ml of water-soluble contrast medium (Omnipaque; Winthrop Pharmaceuticals, New York, NY).[12–14] This cocktail is then emulsified in an equivalent volume of lipiodol. Several embolic agents may be injected in order to enhance the effects of transcatheter intra-arterial drug delivery. The intended purpose of embolization is two-fold: to prevent washout of the drug at the site of tumor and to induce ischemic necrosis. Usually, the injection of embolic particles follows the injection of the chemotherapeutic mixture, yet, some centers favor mixing the particles in slurry with the chemotherapeutic drugs and oil.[11] Gelatin sponge powder and pledgets and polyvinyl alcohol are the most commonly used agents for TACE.[11]

Patient selection and indications for TACE

TACE is a preferred treatment for palliation of unresectable HCC[14–16] and is also employed as an adjunctive therapy to liver resection or as a bridge to OLT, as well as prior to or after radiofrequency ablation.[17–21] However, it is not clear that all of patients with these indications benefit from TACE since in patients with advanced liver disease, treatment-induced liver failure may offset the anti-tumoral effect or survival benefit of the intervention. Key predictors of outcome other than those reflective of tumor burden, such as tumor size, vascular invasion, and α-fetoprotein (AFP) levels, include liver functional impairment (Child-Pugh score, bilirubin), performance status (Karnofsky index, Eastern Co-operative Oncology Group performance status scale), and response to treatment.

The best candidates for TACE are patients with unresectable lesions and preserved liver function, asymptomatic lesions, without vascular invasion or extrahepatic spread. Many prognosticating systems exist for HCC, but the Child-Pugh nominal liver staging system was the most accurate in predicting survival of patients with unresectable HCC treated with TACE,[22] emphasizing the importance of baseline liver function. For many years the use of TACE was based on non-randomized data showing safety and effectiveness of the technique by tumor response (level of evidence: 2 and/or 3).[12,20,23] In 2002, however, two studies showed a statistically significant survival advantage with the use of TACE versus best supportive care in selected patients with well-preserved liver function (level of evidence: 1).[14,16] Llovet *et al.* prospectively studied the survival outcomes in patients treated with fixed interval TACE, trans arterial embolization (TAE) and supportive measures.[14] This trial was stopped early when a survival benefit for TACE became clear. Because the study was discontinued, the TACE vs. TAE question was not answered. In a second randomized controlled trial, Lo *et al.* reported on select patients with unresectable HCC treated with TACE or supportive care and demonstrated that TACE significantly improved survival.[16] In this trial, the most common complications of patients treated with TACE were fever in 32.8%, abdominal pain (26%), vomiting (17%), ascites (5.2%), and gastrointestinal bleeding (4.2%). Other large and small series are consistent with these findings.[20,22,24–28] These results suggest that future prospective randomized studies in advanced HCC should include TACE as the standard of care study arm while comparing equal-risk patient populations. There is now some evidence that patients with portal vein thrombosis (PVT) may tolerate TACE as well. A study by Georgiades *et al.* evaluated the safety of TACE in 32 patients with PVT and identified key prognostic factors and survival.[29] Median overall survival was 9.5 months, and the Child-Pugh numerical disease stage was the prognostic factor most strongly related to survival, while there was no evidence of TACE-related hepatic infarction or acute liver failure.

TACE with drug-eluting microspheres has recently been added to the spectrum of intra-arterial therapies for liver cancer. Drug eluting microspheres injected into the tumor-feeding artery may offer delivery of chemotherapy and embolization with sustained and controlled drug release over time. There are currently two types of microspheres available for drug loading: DC Bead™ microspheres (Biocompatibles, UK) and the recently introduced superabsorbent polymer (SAP) Quadrasphere™ (Hepasphere™ for Europe) microspheres (Biosphere Medical, Inc). These microspheres have different characteristics and can be loaded with a few chemotherapeutics, but are available in the United States only in IRB and FDA Investigational Device Exemption approved trials.

Consensus statement

1. TACE is a standard for intermediate/advanced stage unresectable HCC even in the setting of portal vein involvement (excluding main portal vein)
2. TACE is useful to better select patients for OLT (predictor of tumor biology)
3. There is currently emerging evidence that combination of loco-regional catheter-based approaches and targeted therapy is efficacious and has limited toxicity
4. Technical note: Conventional (oil-based) TACE is likely to be phased out and replaced by drug-eluting microspheres TACE (DEB-TACE).

Systemic therapy of HCC

Sorafenib, a multi-targeted anti-VEGF receptor and raf kinase inhibitor, is approved for the treatment of unresectable HCC[30] based on the results of a double-blinded, randomized phase III trial evaluating sorafenib versus placebo in patients with advanced HCC and Child-Pugh A cirrhosis.[31] This study, known as the SHARP trial, showed an improvement in survival of 10.7 months in the sorafenib group versus 7.9 months in the placebo group ($p < 0.001$, HR = 0.69). Considering the level I evidence this study provides, sorafenib is considered an appropriate choice of therapy for metastatic HCC and locally advanced disease that is not otherwise amenable to a local therapy modality. Despite the improvement in overall survival noted in the SHARP trial, there were few radiographic responses. However, seventy one per cent of patients on sorafenib had stable disease as best response. Data from a phase II study evaluating sorafenib in advanced HCC[32] showed that triphasic CT scans allow an estimate of tumor necrosis/volume ratio, and that this measure correlates with response including stable disease.[33] While prospective studies to test this correlation are being conducted, triphasic CT scan imaging or enhanced MRI are the appropriate modalities to assess response in HCC. AFP plasma level, though not recognized as a surrogate marker for response,[34] may be valuable and complementary in patients whose tumors express AFP.

How to utilize sorafenib in patients with HCC and advanced cirrhosis was the subject of several reported studies. In the phase II study evaluating sorafenib in HCC,[32] 28% of patients had Child-Pugh B cirrhosis. While the pharmacokinetics were comparable for the Child-Pugh A and B patients, there was a more frequent worsening of liver function among the Child-Pugh B patients, represented by an increase in bilirubin in 40% of Child-Pugh B compared to 18% Child-Pugh A patients,[35] although a not harmful inhibitory effect of UGT1A1 leading to decreased bilirubin glucuronidation could partake in this effect. Median time to progression for Child-Pugh A was 21 weeks versus 13 for Child-Pugh B patients, and overall survival was 41 weeks versus 14 weeks, respectively. In a phase I study evaluating two different doses of sorafenib in Japanese patients with advanced HCC,[36] there were no substantial differences in the incidence of adverse events between Child–Pugh A and B groups. In a third study evaluating sorafenib in patients with different malignancies, but with underlying organ dysfunction, the most commonly reported drug-limiting toxicity among patients with elevated bilirubin at baseline was further elevation of bilirubin.[37] It is thus recommended to reduce the sorafenib dose for bilirubin 1.5–3 × upper limit of normal (ULN), and to avoid sorafenib for bilirubin above 3 × ULN. More data are needed to define appropriately the safety and efficacy of sorafenib in patients with HCC and Child-Pugh B cirrhosis, currently the subject of further studies.

Another randomized phase III trial with the same inclusion criteria and design as the SHARP trial was conducted in the Asia-Pacific region in patients with more advanced stage of disease and mainly hepatitis B etiology; there was a statistically significant improvement in survival for sorafenib compared to placebo ($p = 0.014$), but not to the same magnitude as in the SHARP trial.[38] In this study, patients had generally a worse performance status in addition to more extensive disease, which may partly explain the difference in the magnitude of sorafenib benefit between those two studies. There could however be a hepatitis B-related influence on outcome. In a retrospective evaluation of the phase II trial evaluating sorafenib in patients with advanced HCC,[32] there was a trend towards a survival advantage for the hepatitis C (12.4 months) versus hepatitis B patients (7.3 months) (Huitzil *et al.*, ASGO GI Symposium 2008, Abstract 173). A possible HCV-1 core protein associated with an increase in raf kinase activity, suggesting a preferential activity of sorafenib in patients with HCC of HCV origin[39] is supported by a sub-group analysis of patients from the SHARP trial with hepatitis C-associated HCC (Bolondi *et al.*, ASGO GI Symposium 2008, Abstract 129). It was noted that these patients treated with sorafenib had a median survival of 14 months compared to the whole sorafenib treated group of 10.7 months. The outcome of those 18% of patients in the SHARP trial with hepatitis B, however, remains to be reported. Until then, sorafenib remains indicated for all appropriate patients with unresectable HCC, while the underlying hepatitis etiology may be important in future study design.

Several other therapies have been studied as single agent or in combination in advanced HCC, and are being evaluated further in larger phase III trials. Among the anti-angiogenic therapies, bevacizumab has been studied extensively in patients with advanced HCC as single agent,[40,41] or in combination.[41–43] The positive outcome with a combination of bevacizumab and erlotinib, with a median progression free survival of 39 weeks and a median overall survival of 68 weeks,[44] is now being further evaluated in a randomized phase II study that includes a sorafenib monotherapy arm. Sunitinib, another potent anti-angiogenic, was the subject of two single agent studies,[45,46] and is currently being analyzed for superiority in a randomized phase III against sorafenib. ABT 869, an inhibitor of angiogenesis and platelet-derived growth factor receptor function,[47] and brivanib, a dual inhibitor of vascular endothelial growth factor and fibroblast growth factor receptors,[48] are also the subject of large randomized studies. Sorafenib is also

the subject of two large randomized phase III studies, either in combination with erlotinib based on previous phase I experience,[49] or in combination with doxorubicin based on a randomized phase II study (Abou-Alfa *et al*., ASGO GI Symposium 2008, Abstract 128). Unfortunately, this wealth of clinic trials raises a serious question about the use of resources, as HCC remains a relatively rare disease in the United States, and as a consensus on conducting clinical trials that evaluate novel therapies in randomized phase II studies before committing to large randomized phase III studies is needed in order to optimize clinical trial resources.

Due to limited data, the use of sorafenib is currently not recommended outside a clinical trial in the adjuvant or neoadjuvant setting, nor as a bridge to transplant. Recently presented data on the use of sorafenib versus placebo one to three months after TACE have shown no improvement in time-to-progression (5.4 versus 3.7 months respectively, HR = 0.87; 95% CI, 0.70–1.09; p = 0.25) (Okita *et al*., ASGO GI Symposium 2010, Abstract 128), and thus do not support such combined therapy approach in clinical practice. Periprocedural sorafenib at the start of TACE and beyond is currently being studied by an ECOG intergroup trial.[50] An earlier use of anti-angiogenic therapy may be more valuable in curbing the VEGF surge that can be expected after TACE.[51]

Consensus statement

1. Sorafenib is the standard agent for systemic therapy of advanced HCC
2. RECIST criteria are poor parameters for assessing anti-tumor efficacy, but tumor necrosis may be an accurate surrogate if early data can be validated
3. HCC etiology and the extent of cirrhosis influence outcomes of systemic therapies
4. Managing patients with HCC and advanced cirrhosis may require special guidelines
5. Novel systemic agents and combination therapies require further studies

Radioembolization through ^{90}Yttrium microsphere therapy

Growing evidence supports a role of radioembolization for the treatment of HCC, and patients should be selected for this treatment modality by a multidisciplinary team consensus of hepatologists, oncologists, surgeons and interventional radiologists. The emerging role of ^{90}Yttrium (Y90) radioembolization may not just be limited by the stage of the disease.

Radioembolization for patients within transplant criteria

The use of surgical options is the standard for treatment for these patients. Patients within Milan criteria, i.e. a single lesion less than 5 cm or up to 3 lesions all less than 3 cm, are eligible for OLT.[52] Resection is possible only if liver function is preserved. Limited availability of donor organs for OLT and the drop out of patients due to tumor progression limit the number of patients who are able to undergo OLT. Thermal ablation (e.g. radiofrequency ablation) has a limited role due to the risk of tract seeding, and challenges related to size and location of tumors. Radioembolization has been shown to limit the progression of the disease, which can allow the patient more time to wait for donor organs and thus increase their chance of undergoing OLT.[53] Thus, it has a role of bridging patients to OLT.

Radioembolization for patients beyond transplant criteria

The patients who are outside transplant criteria (due to size/number of tumors) but do not have malignant PVT or extrahepatic metastatic HCC may also be candidates for radioembolization. The use of radioembolization in these patients has been shown to downstage the disease to within transplant criteria. This allows patients who were initially outside Milan criteria to become eligible for OLT. There is an increase in overall survival in these patients as well.[53] Lewandowski *et al*. recently published their experience of downstaging using transarterial therapies for HCC.[54] Their data suggest a superior ability of radioembolization to downstage HCC when compared to TACE. The recurrence free survival and overall survival after OLT in the downstaged patients has yet to be compared to that of the patients who were already within transplant criteria to determine the efficacy of downstaging. A thorough radiologic-pathologic correlative analysis has been completed, describing very high rates of complete tumor necrosis at the microscopic level.[55]

Radioembolization for patients with advanced disease

Patients with PVT have been shown to have a favorable response to treatment after radioembolization.[56] The presence of malignant PVT excludes these patients from the transplant criteria, whereas its presence is not a contraindication to radioembolization with Y90. Systemic therapy with sorafenib has been shown to have a statistically significant improvement in survival in patients with advanced disease.[31] The hepatic artery is the sole vascular supply to the parenchyma in the presence of PVT, which renders embolic therapies relatively contraindicated. However, Y90 may be used in these cases due to its minimal embolic effect.[56] A survival benefit (10.1–13.4 months from treatment) has been shown with the use of radioembolization in patients with malignant vascular involvement.[56] A survival benefit, however, has not been shown in patients with distant metastases.[57]

Conclusion

The largest comprehensive analysis on the role of radioembolization for HCC was recently published.[57] The data on 291 patients, substratified by various stages, suggest that radioembolization is a safe and effective treatment modality, with promising response rates and associated survival. Applications of radioembolization include bridging and downstaging potential transplant candidates, as well as palliation in patients with multifocal disease,

particularly those with vascular invasion. Potential advantages over TACE include: a) fewer treatment sessions required, and b) treatment can be performed on an outpatient basis.

Consensus statement

1. Y90 is a safe microembolization treatment and can be administered in the outpatient setting.
2. Y90 could be considered for treating HCC in the following scenarios:
   – downstaging/bridging to transplantation or resection
   – portal vein thrombosis
   – advanced disease.
3. There are no level 1 data for Y90 compared to other regional therapies. Considerations of efficacy and safety (given cirrhosis) have to be made on an individual basis.

Photon and proton radiotherapy

Technological advances and a better understanding of partial liver tolerance of radiation therapy (RT) have improved our ability to deliver tumoricidal doses of RT safely to HCCs, and have led to a resurgence of interest in curative-intent treatment of HCC using RT. Outlined below are the key developments in the use of RT for HCC:

Partial liver irradiation

The development of three-dimensional conformal RT has enabled high dose RT to be directed to the tumor while sparing the non-tumor-bearing surrounding liver parenchyma from these high doses. Using a mathematical model that predicts the risk of radiation-induced liver disease based on dose and fractional volume receiving a given dose, the probability of radiation toxicity can be minimized while still being able to escalate the dose to a small volume.[58]

Image-guidance and targeting

Technological advances in RT now facilitate greater ability to account for respiratory movement of liver tumors during treatment. Tumors can be localized during breathing by using the diaphragm as a surrogate for liver position, via four-dimensional (4D) CT scanning to define the spatial coordinates of the tumor during all phases of respiration, via volumetric cone-beam CT scanning, or using radiopaque fiducials implanted in the vicinity of the tumor. Tumors can be treated during free breathing based on 4D CT derived composite target volumes (coordinates of the tumor during all phases of breathing) or via real-time tracking of tumor motion and gating or robotic control of the treatment beam, during breathholds using active breathing control, or during end-expiratory gating.[59] These techniques improve the precision of radiation delivery and thereby limit collateral normal tissue toxicity.

External beam radiation therapy

Promising clinical data from multiple studies suggest that HCCs are indeed radiosensitive. Sustained local control rates ranging from 71% to 100% have been reported following 30–90 Gy delivered over 1–8 weeks.[59,60] Investigators from Michigan have used conformal RT (1.5 Gy twice daily over 6–8 weeks) with concurrent hepatic arterial fluorodeoxyuridine to treat HCCs safely to doses as high as 90 Gy, with a resulting median survival of 15.2 months.[61] Analysis of these data suggested that doses greater than 75 Gy resulted in more durable in-field local control than lower doses. A prospective French phase II trial administered 66 Gy in 33 fractions to HCCs ineligible for curative therapies and noted 92% tumor responses and 78% 1-year local control rates.[62] Using higher doses and fewer fractions (hypofractionated RT), Canadian researchers have noted excellent local control rates ranging from 70% to 90% when the radiation beam can be directed from multiple planes (stereotactic RT) converging on the tumor, the majority of the liver can be spared from irradiation, and treatment is image-guided.[60,63,64] Across all partial liver radiation paradigms, the most common site of first recurrence is intrahepatic, however outside the high dose-irradiated volume; toxicity is greater in Child-Pugh B compared to Child-Pugh A patients.

Proton irradiation

In contrast to photon irradiation, where the dose delivered to the tumor is limited by the entrance and exit doses that can potentially harm normal tissues, accelerated proton beams deposit dose within the tumor without exiting through normal tissues beyond the tumor. Japanese investigators have reported results of treatment with 72 Gy in 16 fractions of proton beam therapy for 162 patients with 192 unresectable HCCs.[65] The 5-year local control rate of 87% and overall survival rate of 23.5% in the absence of significant toxicity are clinically noteworthy. Furthermore, the impressive 5-year survival rate of 53.5% achieved in a subset of 50 patients with solitary tumors and Child-Pugh A cirrhosis suggests that proton beam therapy is safe and efficacious in the treatment of HCC, and that the results may compare favorably to other curative treatments. Other groups have reported similar results with proton beam therapy of HCCs as well.[66,67]

Combination of RT with other therapies

Tumors treated with TACE, an established treatment for unresectable HCC, often do not achieve durable local responses.[68,69] RT has been combined with TACE to overcome treatment resistance. Korean researchers initially noted >60% response rates and a significant drop in tumor markers levels using this combination treatment strategy.[70,71] TACE followed by RT was reported to improve overall survival over TACE alone in a retrospective analysis of this experience. Similar results have been reported by other groups.[72–74] To address the persisting challenge of out-of-field intraheptic failures despite improved in-field local control, concurrent intra-arterial 5-FU and RT followed by monthly 5-FU and cisplatin has shown some promise.[75]

Treatment of unfavorable tumors

Multiple groups have reported favorable outcomes in patients with tumoral PVT treated with RT.[60] Response rates range from

37.5 to 100%, and median survival durations range from 3.8 to 10.7 months.[60] Proton beam therapy has also been safe and effective in the treatment of patients with limited treatment options, i.e. recurrent HCCs after prior proton therapy, tumoral PVT, and Child-Pugh Class C cirrhosis.[59]

Consensus statement

1. Radiation therapy can provide local control for some unresectable HCC lesions.
2. Improved understanding of partial liver RT tolerance and better RT planning and delivery have advanced the ability to escalate radiation dose to unresectable HCCs without causing undue toxicity.
3. Hypofractionation, stereotactic treatment and proton beam therapy are further expanding the horizons of treatment.
4. Strategies that combine RT with other therapies merit continued evaluation.

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Conflict of interest

None declared.

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